line value by day 16. DNA sequence analysis of the NS5B gene derived from chimp serum is currently in progress to determine if mutations associated with ANA598 drug resistance are present. Conclusion: ANA598 exhibits substantial inhibitory effect against HCV genotype Ia and 1b virus in HCV infected chimpanzees following single and multiple oral doses and was well-tolerated throughout the course of the study. Plasma concentrations sufficient for antiviral activity are readily achievable in HCV infected chimpanzees with oral administration of ANA598. The favorable profile of ANA598 observed to date supports its continued development as a candidate for use in combination with other agents for the treatment of chronic HCV infection.

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IN VITRO STUDIES DEMONSTRATE THAT COMBINATIONS OF ANTIVIRAL AGENTS THAT INCLUDE HCV POLYMERASE INHIBITOR ANA598 HAVE THE POTENTIAL TO OVERCOME VIRAL RESISTANCE

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<p>**BACKGROUND:** ANA598 is a novel HCV non-nucleoside polymerase inhibitor that is in clinical development for the treatment of hepatitis C. Due to the high potential for developing resistance to any direct antiviral used as monotherapy in hepatitis C, it is believed that optimal use of direct antivirals will be in combination regimens designed to minimize emergence of resistance. Therefore, it is important to assess combinations of agents for absence of antagonism, characterize *in vitro* patterns of resistance to new direct antivirals, identify agents which retain full potency to the characterized mutations, and determine if new antivirals possess activity against mutations known to confer resistance to other agents. This information will enable future clinical exploration of optimized combination regimens. **RESULTS:** ANA598 exhibits nanomolar potency against genotype 1 HCV replicons (EC_{50} 1b 3nM; 1a 50nM). We utilized *in vitro* assays to explore the potential of combining ANA598 with other anti-HCV agents, including current standard of care (SOC) as well as direct antivirals currently in development. ANA598 was shown to be highly synergistic with IFN-α and not ontagonistic with ribavirin. No change in susceptibility was observed when ANA598 was tested with replicons containing the primary mutations known to confer resistance to other direct antivirals including A156T (NS3 protease active site), S282T (NS5B nucleoside binding site) and M423T (NS5B non-nucleoside thumb binding site). Genotypic mutations resistant to ANA598 (M414T, M414L, G554D, and M414T/G554D) were identified *in vitro*. Reduced potency was observed for ANA598 against all four mutations with EC_{50} values of 0.47, 0.30, 0.63 and 20μM determined for M414T, M414L, G554D, and M414T/G554D, respectively. In contrast, replicons containing mutations that confer resistance to ANA598 remained fully susceptible to IFN-α, VX-950 (NS3 protease inhibitor), and NM107 (nucleoside polymerase inhibitor). **CONCLUSION:** These preclinical results suggest the potential to construct useful combination treatments containing ANA598 and other anti-HCV agents. Combinations of ANA598 with components of current SOC are favorable regimens for clinical testing based on the high degree of synergy with IFN-α and the lack of antagonism with ribavirin. ANA598 in combination with other direct antivirals are of interest based on the lack of cross resistance to several agents, including protease, nucleoside and certain non-nucleoside inhibitors. In the future, appropriately constructed combination regimens may confer clinical benefit by improving response rates and allowing current non-responders to be treated more effectively.

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1909
IDENTIFICATION OF NOVEL NON-MACROCYCLIC INHIBITORS OF HCV NS3/4A SERINE PROTEASE ACTIVITY

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Background: Agents that target the serine protease activity of NS3/4A have emerged as potentially significant components of therapies targeting the HCV virus. An agent's dosing convenience, side effect profile, and efficacy all bear on its clinical utility. Here we describe a non-macrocyclic compound that has emerged from our ongoing drug discovery efforts involving macrocyclic and non-macrocyclic protease inhibitors. The performance characteristics of this compound, ITMN-5489, compare favorably with ITMN-191, the latter compound having recently demonstrated robust antiviral activity and promising safety in initial clinical studies. Methods: Structure guided drug design was used in a campaign to refine potency, ADME properties and exposure in animals. Results: Ongoing discovery efforts have identified a series of non-macrocyclic compounds with favorable in-vitro and pharmacokinetic characteristics. Among these, ITMN-5489 displays an EC50 of ~1 nM against a genotype 1b replicon and 81 nM provides HCV replicon clearance in 14 day antiviral assays. The profile of inhibition against of a panel of 79 proteases and other cellular proteins suggests that off-target effects would compare favorably to several NS3/4A inhibitors currently in clinical development. ITMN-5489 exhibits significant stability in hepatocytes derived from rat, monkey and human, and plasma protein binding is uniform across these species. In primates, plasma exposure of ITMN-5489 compares favorably to that of ITMN-191. ITMN-5489 plasma concentrations 24 hours after dosing are higher than the 12 hr post dose concentration of ITMN-191 and overall AUC is 5 to 10 fold higher for ITMN-5489. Primate liver exposure of ITMN-5489 is > 7 fold higher than that of ITMN-191, and its liver to plasma ratio is approximately 60. Conclusions: In short duration clinical studies, administration of ITMN-191 under both q12h and q8h schedules has shown very favorable virologic response and safety profiles. Here, we report a novel inhibitor of NS3/4A with in-vitro and pharmacokinetics characteristics, including exposure in primate that compare favorably to ITMN-191. ITMN-5489, like ITMN-191, shows a significantly higher concentration in liver as compared to plasma. Both plasma and liver exposure of ITMN-5489 are higher than those of ITMN-191, suggesting lower doses of this agent may achieve similar antiviral effect. The significant con-